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Description

Composition of a transdermal delivery system, which modulates inflammation, via insitu systems, thereby promoting repair of injured, damaged or diseased joints, and soft tissue.

BACKGROUND OF INVENTION

[0001] *Current U.S. Class: 514/310; 424/59; 424/61; 424/70.1; 424/400; 424/450; 424/489; 514/159; 514/256 International Class: A61K 031/47 Field of Search: 424/59,61,78,480,489,70,400 514/159,254,310*

[0002] References Cited [Referenced By] U.S. Patent Documents: US4968685 1990-11 Grollier L'Oreal Composition for inducing and stimulating hair growth and retarding its loss, based on nicotinic esters and pyrimidine derivatives US5133958 1992-07 Stuckler Agent for nail, skin and hair care US5215759 1993-06 Mausner Chanel, Inc. Cosmetic composition US5318960 1994-06 Toppo Toppo; Frank

System for transdermal delivery of pain relieving substances US5954675 Method of ultrasonic therapy 1999-09-21 US5496827 Compositions for the transdermal delivery of nutrients 1996-03-05 US5451407 Reduction or prevention of skin irritation or sensitization during transdermal administration of a irritating or sensitizing drug 1995-09-19 US6398753 Ultrasound enhancement of percutaneous drug absorption 2002-06-04 US6316490 Substituted aryl compounds useful as modulators of acetylcholine receptors 2001-11-13 US6283956 Reduction, elimination, or stimulation of hair growth 2001-09-04 US6194581 Substituted pyridines useful as modulators of acetylcholine receptors 2001-02-27 US6030374 Ultrasound enhancement of percutaneous drug absorption 2000-02-29 US5985860 System for transdermal delivery of pain relieving substances 1999-11-16 US5723477 Modulators of acetylcholine receptors 1998-03-03 US5705512 Modulators of acetylcholine receptors 1998-01-06 US5703100 Modulators of acetylcholine receptors 1997-12-30 US5677459 Methods for the preparation of modulators of acetylcholine receptors 1997-10-14 US5594011 Modulators of acetylcholine receptors 1997-01-14 US5240945 Method and composi-

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[0098] *Field of the invention:* The present invention relates to the field of nutritional biochemistry and further to a transdermal method for delivery of nutrients. This provides the body with required nutrients, which thereby enable the in-situ systems to modulate inflammation, thus repair injury, damaged or diseased joints, and soft tissue as a result of oxidative insult, stress, injury or disease.

[0099] *Background of the invention*: Inflammation is a reaction of living tissues to injury. The discipline of pathology makes a fundamental distinction between acute and chronic inflammation. Acute inflammation comprises the immediate and early response to an injurious agent and is basically a defensive response that paves the way for repair of the

damaged site. Chronic inflammation results from stimuli that are persistent.

[0100] Arachidonic acid plays a central role in a biological control system where such oxygenated derivatives as prostaglandins, thromboxanes, and leukotrienes are mediators. The leukotrienes are formed by transformation of arachidonic acid into an unstable epoxide intermediate, leukotriene A4, which can be converted enzymatically by hydration to leukotriene B4, and by addition of glutathione to leukotriene C4. This last compound is metabolized to leukotrienes D4 and E4 by successive elimination of a gamma-glutamyl residue and glycine. Slow-reacting substance of anaphylaxis consists of leukotrienes C4, D4, and E4. The cysteinyl-containing leukotrienes are potent bronchoconstrictors, increase vascular permeability in postcapillary venules, and stimulate mucus secretion. Leukotriene B4 causes adhesion and chemotactic movement of leukocytes and stimulates aggregation, enzyme release, and generation of superoxide in neutrophils. Leukotrienes C4, D4, and E4, which are released from the lung tissue of asthmatic subjects exposed to specific allergens, seem to play a pathophysiological role in immediate hypersensitivity reactions. These leukotrienes, as

well as leukotriene B4, have pro-inflammatory effects. Leukotriene B(4) (LTB(4)) is a potent, proinflammatory mediator involved in the pathogenesis of a number of diseases including psoriasis and rheumatoid arthritis.

[0101] Proprietary formulations of the amino acid L-histidine are under development as pharmaceutical agents because of the molecule's antioxidant and anti-inflammatory properties. L-histidine has been well characterized in terms of probable dietary requirements, plasma and tissue concentrations, pharmacokinetics, metabolism and excretion, and medical conditions related to physiologic handling. Previous experience with histidine dosing in the literature is extensive, and both clinical and preclinical data suggest that histidine administration is very safe. L-histidine has been shown to scavenge both the hydroxyl radical and singlet oxygen (102) in many studies. These interactions may involve free histidine, small histidine-containing peptides such as carnosine, and histidine residues in proteins. Histidine appears to interfere with redox reactions involving iron and perhaps other metal ions and to interact directly with 102; the ability of histidine to scavenge 102, a toxic oxygen species of increasing concern, has been well established in the laboratory. Many recent studies have

demonstrated the therapeutic efficacy of "pharmacologic" doses of L-histidine in animal models of inflammatory conditions, particularly gastrointestinal conditions and cardiac ischemia-reperfusion injury, and have specifically linked the anti-inflammatory capabilities of histidine to its ability to scavenge toxic oxygen species. The maintenance of histidine pools, therefore, may contribute to the body's physiologic antioxidant capacity. Taken together, the data suggest that histidine supplementation could provide a safe, efficacious method to increase antioxidant protection.

[0102] Endogenous L-carnosine is a di-peptide, synthesized in the mammalian tissue and brain by an enzyme, carnosine-synthetase, which bonds the amino acids beta-alanine and histidine. The enzyme carnosinase, maintains carnosine equilibrium (inactivates) by cleaving the peptide bond in the plasma. This yields the amino acids beta-alanine and histidine. The half-life of carnosine in plasma is about one minute. The only mammals that maintain plasma carnosinase are humans, primates and the Syrian Golden Hamster.

[0103] Carnosine seems to be concentrated in actively contracting muscles. In patients with degenerative disease, for ex-

ample MS or muscular dystrophy, carnosine levels are lower.

[0104] The concentration of carnosine in muscles also appears to correlate with age. Older people have lower levels of carnosine in their muscles. Carnosine is an anti-aging product because of its effects on advanced glycosylation end-products or AGE's. AGE's are abnormal, cross-linked and oxidized proteins that play a role in the aging process. Carnosine appears to block the formation of AGE's and ensures the proper formation of proteins on the DNA level. For this reason there is great interest in using carnosine for the complications of diabetes, such as cataracts, neuropathy and kidney failure, which all arise from glycosylation.

[0105] Carnosine has anti-carbonylation qualities, which prevents the age-related degradation of the body's proteins. Carnosine is a potent antioxidant, which effectively quenches the most destructive of the free radicals -- the hydroxyl radical and the peroxyl radical.

[0106] Carnosine also has a remarkable ability to rejuvenate cells approaching senescence -- restoring normal appearance and extending cellular lifespan. As a wound healing agent carnosine has the ability to rejuvenate connective tissue.

Additionally it protects the brain from plaque formation that leads to senility or Alzheimers disease. Carnosine enables the heart muscle to contract more effectively through enhancement of calcium response in heart myocytes. It also protects cellular DNA from oxidative damage, which accumulates with age. Finally, carnosine helps prevent skin collagen cross-linking which leads to loss of elasticity, wrinkles, macro-molecular disorganization and loss of extra-cellular matrix. Carnosine extends the functional life of the body's key building blocks, cells, proteins, DNA, lipids and is an agent of longevity. Besides reversing the signs of aging in cells approaching senescence and increasing cellular life span, studies show that carnosine is effective against all forms of protein modification. Carnosine levels decline as we age. Muscle levels drastically decline over 63% from ages 10 to 70, which accounts for the normal age related decline in muscle mass and function.

[0107] Carcinine, also a di-peptide (resistant to hydrolysis by carnosinase) is synthesized from beta alanine and histamine. First, histidine is metabolized by histidine decarboxylase (not found in the eyes) into histamine. Carcinine synthetase (an abundant, stable enzyme) bonds beta ala-

nine and histamine to produce carcinine. The seat of carcinine synthesis is the CNS (Central Nervous System) where carcinine synthetase is 15 times higher than elsewhere. Carcinine is an antioxidant di-peptide that specifically addresses CNS oxidation. Additionally, carcinine a catabolic metabolite of histamine accumulates in the heart after completing its function in the CNS thereby increasing cardiac output.

[0108] With beta alanine, L-histidine and its metabolite histamine introduced locally, at the site of affliction, it is logical to assume that these tissues and cells will take up these molecules and synthesis carnosine and/or carcinine.

SUMMARY OF INVENTION

[0109] The present invention pertains to a medicating composition for dermal application comprising methyl nicotinate, nicotinic acid, alpha lipoic acid, beta alanine, histidine, carnosine, copper, pyridoxal-5-phosphate, medium chain triglycerides, phosphatidyl choline, glycerol, polysorbate 80, propylene glycol, and water. This composition of nutrient co-factors is applied locally via a trans-dermal method. This provides the insitu system's of the body with required nutrients to control inflammation and repair injured, damaged or diseased joints, and soft tissue as a re-

sult of oxidative insult, stress, injury or disease. Each of the ingredients serves as a co-synergist in a series of intertwined biochemical loops to substantiate each individual ingredient and to form a positive synergistic response operating in concert.

[0110] Typical dosage/usage will depend on factors such as size, age, health of the user, and nature of the inflammation, along with location and duration of the injury/event. This treatment is effective when administered on a chronic or acute basis contingent on the duration, severity and physical rehabilitation of the injury/affliction.

DETAILED DESCRIPTION

[0111] Methyl nicotinate is present for its ability to easily and consistently pass through the epidermis and as such carry with it nutrients to the target area, there-by by passing the G. I. tract and liver. This eliminates the usual degradation and metabolism associated with oral ingestion. Nicotinate increases the surface temperature of the skin (warming) and causes a significant release of prostaglandins (PGE 2) from the skin, as well as stimulating histamine release from the of the mast of the cells in the tissue thereby initiating the autacoid response of the specific immune system. This facilitates blood circulation

to and then away from the site of an injury. Increased circulation facilitates the repair process by supplying needed molecules and removing deleterious ones. Methyl nicotinate also interacts with other members of the nicotinoid super-family and produces a catalyzing effect on the absorption of nutrients and expeditious transport of nutrients to deep soft tissues and joints.

[0112] Nicotinic acid is used as a complement to methyl nicotinate. Nicotinic acid is used topically to act as an additional electron donor from which to draw upon for heightened tissue repair. Nicotinate forms its own biochemical loop interacting with the epidermis and creating a "skin-flush", as well as, co-synergizing with P-5-P, methyl nicotinate, and copper.

[0113] Nicotinic acid receptors know as the G-Protein-Coupled Receptor G(1) are highly expressed in adipose tissue. By including both methyl nicotinate and nicotinic acid in this formula there is a 2 pronged "time released" effect on G(1). This serves to stimulate the release of fatty acids from the adipose tissue. Adipose tissue contains (stores) various fatty acids - one of which is arachadonic acid (AA). AA is the main constituent of the autacoid - prostaglandins, part of the specific immune system which

initiates the repair process. The combination of these nicotinoids provides the formulation with the beginning of a healing loop to undo the internal oxidative insult due to injury or atrophy.

[0114] Pyridoxol -5- Phosphate is a potent and active form of Vitamin B-6. P -5- P is a vital cofactor - necessary in the methylation process, which is endemic in the biochemical process called "Life". By directly introducing P -5- P, where it is needed - through a trans-dermal system we have eliminated the associated degradation resulting from oral ingestion and the concomitant pass through the GI tract and liver. P -5- P can work as a catalyst with the requiste enzymes, amino acids and other nutrients/vitamins to produce a reaction(s).

[0115] P -5- P is required for the absorption and movement (transport) into the bloodstream and tissue of amino acids - as such it is a conduit provider. P -5- P forms its own facilitator loop allowing for greater biochemical uptake of copper, as well as, the amino acids beta alanine and L-histidine. Of other importance, P -5 - P (as an antioxidant) minimizes "free" copper from oxidizing HDL cholesterol more effectively than vitamin E. It helps to ensure copper's utility in the formulation and increases its

transport and bio-availability. Thus, P -5- P forms a conduit loop, an antioxidant loop, a methylation loop while catalyzing histidine into histamine and further into carcinine.

[0116] Alpha-Lipoic Acid - as a thiol ALA is a universal antioxidant, which interacts with other water and fat-soluble antioxidants. ALA potentiates them and increases their respective bio-absorbability by serving to re-cycle these anti-oxidants. forms an exceptionally strong antioxidant loop while interacting with-5- P, copper, histidine, beta alanine, methyl nicotinate and nicotinic acid substantiating the respective antioxidant benefits of those nutrients and acting as a biochemical overseer for anti-oxidation and free radical quenching.

[0117] ALA also works along with the nicotinates to seamlessly pass through the skin barrier and protect and buffer any and all metabolic by-products deposited beyond the plasma membrane; in this way it serves both as an antioxidant loop coordinator and becomes a vital part of the intra-epidermal transport loop. ALA serves as a prosthetic group, a scaffold of the H-protein of the glycine cleavage system and the dihydrolipoamide acyltransferases (E2) of the pyruvate, alpha ketoglutarate and branched-chain al-

pha-keto acid dehydrogenase complexes. ALA and its reduced form, di-hydrolipoic acid scavenges ROS (reactive oxygen species). ALA has proven beneficial clinical effects on oxidative stress models by blocking the reuptake/ reactivation of the neuro-toxic glutamate metabolites.

[0118] Copper - A ubiquitous mineral, copper, is utilized by the body in a variety of ways. When added to this present composition copper provides an analgesic-like effect to the structures deep within the joint and soft tissues. Copper provides the biochemical infrastructure and scaffolding for the universal anti-oxidant, one of the body's principal free radical scavengers, superoxide dismutase (Cu SOD).

[0119] Copper is an element necessary for oxidation and absorption of iron and vitamin C (ascorbic acid) in digestion. Copper also acts as a catalyst in the formation of hemoglobin , the oxygen-carrying blood component, and a condition similar to iron-deficiency (anemia) has been produced experimentally in cases of copper deficiency. Thus, copper serves as an antioxidant loop, part of the overall healing loop and a part of the pain diminishment loop. Working in synergy with P -5- P free copper is made safe, non-toxic and bioavailable to become SOD - coun-

tering oxidative tissue and joint insult.

[0120] L-Histidine forms its own loop with respect to entry. As a potent anti-oxidant histidine is also a pro-stimulator of circulation when topically applied. But, much more as a co-synergist with several other substrates to form a histidine - histamine - carcinine - carnosine loop, protecting tissues from further oxidative stress/damage while providing a readily available scaffold for neural-transmission and pain mitigation. Histidine acts as a neuro-modulator, secondary neurotransmitter, neuro-protectant against hydroxyl radicals, a cellular homeostasis regulator and anti-inflammatory agent.

[0121] The carnosine loop elucidated is such. Histidine in the presence of beta alanine, ATP, and carnosine synthetase is metabolized to yield carnosine. Carnosine is a biologically super-active peptide, with a multitude of functions. Carnosine synthetase is found in tissue both slow twitch and fast twitch. This is where carnosine is synthesized.

[0122] This is also where carnosine effects are most required. This method of trans-dermal, local introduction into tissue cells - histidine and beta alanine - tissue that contains carnosine synthetase, for the expressed, expedited purpose of synthesizing carnosine - where it is most

needed - is indeed novel.

[0123] The metabolism of carnosine loop elucidated is such. Carnosine, a peptide is metabolized by carnosinase in the plasma. Yielding histidine and beta alanine which may then again be synthesized back into carnosine, however carnosine synthetase is needed, this enzyme is an enzyme that is under-abundant and unstable. This fact is expressed to limit the availability and quantity of carnosine.

[0124] An alternative metabolic process for histidine is into histamine. Histidine in the presence of histidine decarboxylase - with the required cofactor P-5-P is metabolized into histamine. Histamine, in its own right is a super-potent anti oxidant, anti-inflammatory, neuro modulator, neuro-protectant, neuro-transmitter amino acid. Like its sister molecule histidine, histamine has a multitude of biological functions. When histamine is present it is able to exert its activity as histamine, or it can be metabolized into carcinine.

[0125] Carcinine is synthesized in the presence of carcinine synthetase, histamine, beta alanine, ATP and the required cofactor P -5- P. Carcinine a potent anti oxidant is primarily active in the CNS (central nervous system). It has been shown that carcinine synthetase enzyme levels are 15

times higher in the CNS than elsewhere. The seat of carcinine synthesis and activity is the CNS.

[0126] After carcinine has exerted its activity as an anti oxidant in the CNS it is transported away in the plasma resulting in a smooth-muscle relaxatory effect, which lowers blood pressure. Additionally, carcinine as an anti oxidant accumulates in the heart expressing its activity there. Carcinine can be metabolized back into histamine and beta alanine, also by carnosinase, however, it is relatively resistant to its effects. Histamine and beta alanine are both oxidized into acetic acid. Additionally histamine could remain as histamine retaken up in the carcinine loop, or methylated into 3 methylhistamine.

[0127] The vast majority of histamine is methylated then oxidized to imidazole acetic acid, a molecule that can occupy the glycine receptor - preventing glutamate activity. Glutamate, an excitatory amino acid responsible for the "Pain Signal" cannot send the pain signal unless glycine occupies its receptor at the same time.

[0128] Histidine as you can understand, is therefore involved in its own neuro-hormonal loop, a synergized breakdown-conversion loop and an anti-inflammatory loop. Together with P -5- P and the nicotinoids, histidine forms a power-

ful inflammatory cascade and resulting / subsequent anti-inflammatory loop. By engendering the formation of site specific prostaglandins - tissue and joint insult is rapidly mitigated and systemic healing / replacement is permitted to occur at a much more rapid rate.

[0129] Beta alanine - the predominate branch amino acid in mammals and also the only naturally occurring branch amino acid is part of its own loop, the regenerating keratin loop - a constituent of the major molecular ingredient of human skin - keratin. Additionally, it is known to stimulate collagen (constituent of cartilage and platelets) and nucleic acid synthesis.

[0130] Beta alanine is an essential co-factor for the carcinine-carnosine loop- efficacious as an anti-oxidant and for the cellular regulation/repair process. Beta alanine together with histidine/histamine forms the carnosine-carcinine covalent bond. Beta alanine is a key molecule necessary for production of carcinine - found almost exclusively in the central nervous system (CNS) and acts as an arbiter and anti-inflammation regulator, antioxidant and neuro - modulation agent.

[0131] Beta alanine is also a key molecule necessary for production of carnosine, a vital part of this multi-clustered loop.

Carnosine acts as a very powerful wound- healing agent, exhibiting anti-senescent effect at the cellular level. As well as, a potent time-dependent regulator of the intra-cellular "biological-clock" cascade, also serving as an au-toimmune function protector.

[0132] Beta alanine additionally is a necessary component for the synthesis (non-vertebrates) of pantothenic acid (B5), which is a cofactor needed for the synthesis of Co A. Co A, a very interesting enzyme, initiates the Krebs cycle. The Krebs cycle is the system in the body that produces ATP (adenosine tri phosphate) energy. This cycle of energy is the most basic molecular production of energy in all cells of the body. Interestingly, injury and exercise deplete cells of ATP. ATP depleted cells, "pre-loaded" with beta alanine stimulates the uptake of beta alanine, and thus the "Krebs Cycle" and repair process.

[0133] Beta alanine, completely desensitizes the glycine receptor and then metabolizes into acetic acid - a molecule which is also able to occupy the glycine receptor. This receptor occupation prevents the neuron from sending a gluta-mate-induced signal a signal that results in feeling pain. With the glycine receptor occupied by acetic acid, the metabolite of beta alanine, a concomitant cessation of

glutamate excitation is prevented. This prevention minimizes NMDA neuro-toxicity, a metabolite of glutamate excitation, allowing for a quick, utilizable uptake of the formulation substrates.

[0134] Leukotrienes B4 are the predominant pro-inflammatory molecule in the body. Leukotrienes B4, metabolites of arachadonic acid are rapidly, potently suppressed by beta alanine. Hence, this method of delivery of beta alanine and its ability to suppress leukotriene initiated inflammation is indeed novel.

[0135] Medium Chain Triglycerides - are involved in the surface absorption of the formulation and play a vital role in the ability of this formulation to pass thorough the skin's plasma membrane and also act as a carrier, bringing nutrients to injured joints and tissues. They improve and enhance the trans-dermal delivery of nutrients and as such are involved in the transport loop of the formulation.

[0136] Propylene Glycol and Polysorbate 80 - are both non-ionic solvents, which serve as coupling agents in the formulation. They are both used principally in the transport loop. Both provide for the marriage and transport of water, nutrients and oils (MCT's) by acting as a bridge and conduit between the glycerol backbone of the MCT's and the wa-

ter. Thus, permitting the oil, water, and nutrient mixture to restructure its molecular makeup and become one, while passing through the epidermis and dermis into the tissue, joint, cells, ultimately into the plasma. While allowing the nutrients as well as the metabolites to be become systemic, thereby allowing the required environment to be created for the desired healing / repairing processes.

[0137] Glycerol - is hydroscopic and acts as a moisturizing agent, more directly as a method to open this solutions' molecules, enabling better, more complete uptake through the pores of the skin, which allows better reception of the formulations substrates. Thus, glycerol is part of the transport and initial delivery loop. It provides the first entry into the skin barrier where propylene glycol and polysorbate-80, as well as, MCT's take over to provide a secondary transport and delivery system.

[0138] A transdermal healing composition has been described with reference to a particular embodiment. For one skilled in the art, other modifications and enhancements can be made without departing from the spirit and scope of the aforementioned claims.

[0139] Whilst endeavoring in the foregoing specification to draw attention to those features of the invention believed to be

of particular importance it should be understood that the Applicant claims protection in respect of any patentable feature hereinbefore referred to whether or not particular emphasis has been placed thereon.